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TYPES OF PHARMACOLOGICAL ACTION AT AUTONOMIC GANGLIA

BY

W. D. M. PATON

(Arch. int. Pharmacodyn.)

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TYPES OF PHARMACOLOGICAL ACTION AT AUTONOMIC GANGLIA (¹)

BY

W. D. M. PATON

(Received for publication 27-2-1954*)*.

A wide range of drugs is now known or believed to affect transmission in autonomic ganglia, yet it is only for a few of them that we have a clear picture of the action involved. Now there are several reasons why it is important to have such a picture :

1. Their clinical use cannot be fully exploited without it.

2. Ganglionically active drugs are increasingly used as research tools—for instance to test whether autonomic elements are involved, or to exclude autonomic reactions from a response. For this purpose one must understand not only the principal action of the drug concerned, but also have some sort of quantitative estimate of its other actions—i.e. an estimate of its *specificity*. If one accepts as a specific drug one whose main action is exerted in a dose 100 times smaller than any other action, then few drugs indeed are specific—certainly not such familiar friends as atropine, nicotine or *d*-tubocurarine. Yet a criterion of this sort is not unreasonable—drugs are quite often used in concentrations 100 times greater than threshold for the action considered.

3. The actions of a drug are themselves of biological interest, representing as they do the reaction of an organism to a particular chemical stimulus. But if one is analysing a particular aspect of the function of the organism in this way, obviously one's progress depends directly knowledge about the actions of the drug used.

(¹) Paper presented at the International Meeting of Pharmacology at Montreal.

4. Lastly, the attempts to associate particular chemical structures with particular actions, already sufficiently confusing, become nearly hopeless unless one is certain that each of the drugs so associated has in fact the same action : an obvious example is the danger of confusing, among drugs active at the neuromuscular junction, those acting competitively and those producing a persistent endplate depolarization.

I shall try, therefore, to discuss one problem which arises the moment one begins to try to be precise about ganglionic actions; this is : " What are the actions that need to be considered ? " This paper will attempt a sort of résumé of the types of action that one knows of or suspects, together with an enumeration of representative drugs in each group.

METHODS OF ANALYSIS

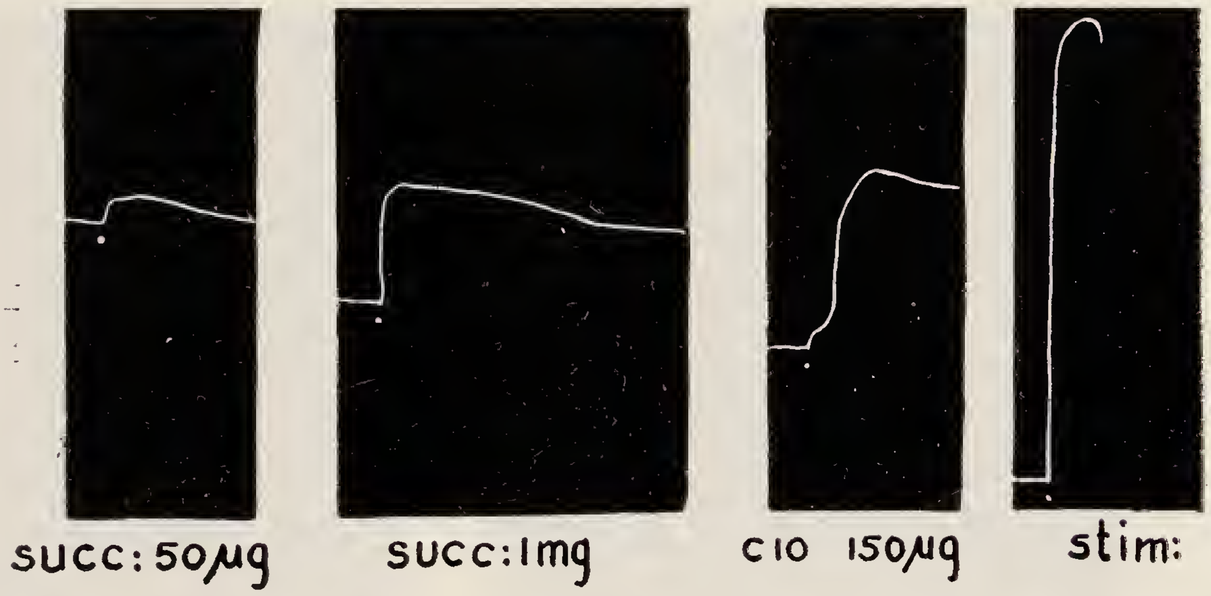
It is worth mentioning first, however, some of the difficulties that lie in wait for the unwary investigator. There are two typical difficulties :

a) the proof of ganglion-stimulation;

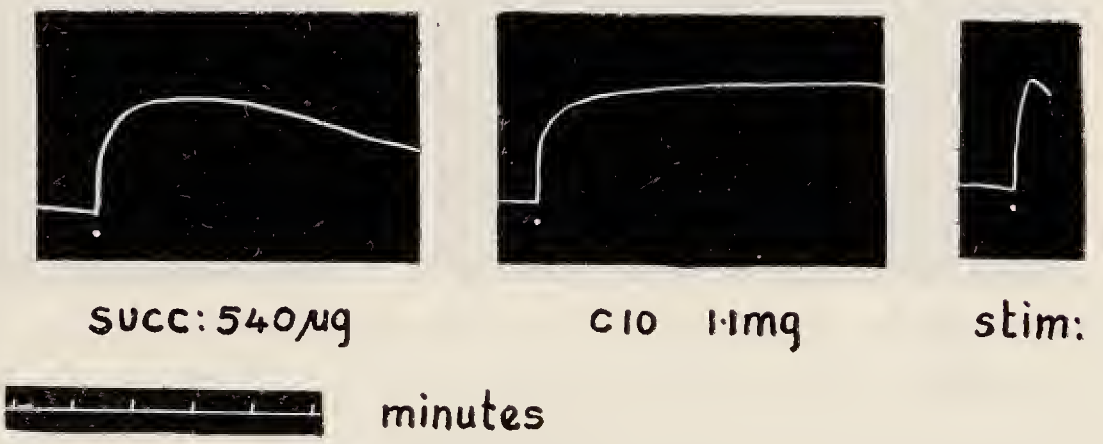
b) the test for action on acetylcholine release.

As regards the first, the main problem is to exclude the possibility that the apparent stimulant effect is not on the ganglion but on some peripheral receptor structure. Thus, if the superior cervical ganglion and nictitating membrane are used, a retraction of the membrane can be produced not only by ganglionic excitation but also by adrenaline-like actions, by muscarinic actions, and (through fascial connections with the external ocular muscles) by stimulants of striated muscle (FIG. 1). (PATON & THOMPSON, 1953, unpublished). Even the use of the isolated perfused ganglion *in situ* is not always safe; for we have found that as much as 50 % of perfusate may fail to appear in the venous effluent or in the edema round the ganglion, but has presumably found arterial or venous channels into the animal. Further, by injection of dyes one can show an anastomosis, through the fine vessels of the postganglionic trunk, with the blood vessels of the bone of the skull which might well (in an upredictable way) finally lead perfusion fluid to the muscular structures in the orbit. It is for this reason that a number of precautions (to be described by Dr. AMBACHE) are essential, which need to be carefully framed for each set of circumstances.

A much more rigorous test of ganglion stimulation is to use electrical recording to reveal the presence or absence of depolarization of the ganglion, but of course the technique is somewhat elaborate. Another test which does not seem to have been used before is to compare the responses on both sides of the animal, when the S.C.G. had been excised on one side (FIG. 2).



Cat



Dog

FIG. 1

Contractions of the nictitating membrane produced by stimulants of the striated muscle motor endplate. Above, responses in the cat (under chloralose) to Succinylcholine (50 μg and 1 mg), and, in another animal to decamethonium (150 μg) and to maximal stimulation (10 c/s) of the cervical sympathetic.

Below, responses in the dog (chloralose-urethane) to Succinylcholine (50 μg/kg) and to Decamethonium (100 μg/kg), and finally to maximal stimulation (10 c/s) of the cervical sympathetic.

Contractions due to motor endplate stimulants are not prevented by hexamethonium or by excision of the S.C.G., but can be selectively abolished by small doses of a specific competitive neuromuscular blocking agent such as *d*-tubocurarine-methylether.

Secondly, as regards testing the output of acetylcholine by a ganglion, this is a somewhat elaborate experiment which is sometimes avoided; the only way of doing it is still by the method of KIBJAKOW (1933) and FELDBERG AND GADDUM (1933). One might argue that if a drug causes block of ganglionic transmission, and if it can also antagonise the ganglion stimulating effects of acetylcholine or of nicotine, then the antinicotine effects can be assumed to account for the block observed; thus it might be thought to be unnecessary to test for effect on acetylcholine release. But this deduction does not follow, because no one can yet estimate quantitatively from an anti-nicotine action how great the blocking action of a compound on normal transmission will be; further, anti-release and anti-stimulant actions are certainly not mutually exclusive, for compounds are known to exist (notably local anaesthetics) which possess *both* actions. It seems inevitable, therefore, that the direct experiment on acetylcholine output must be made.

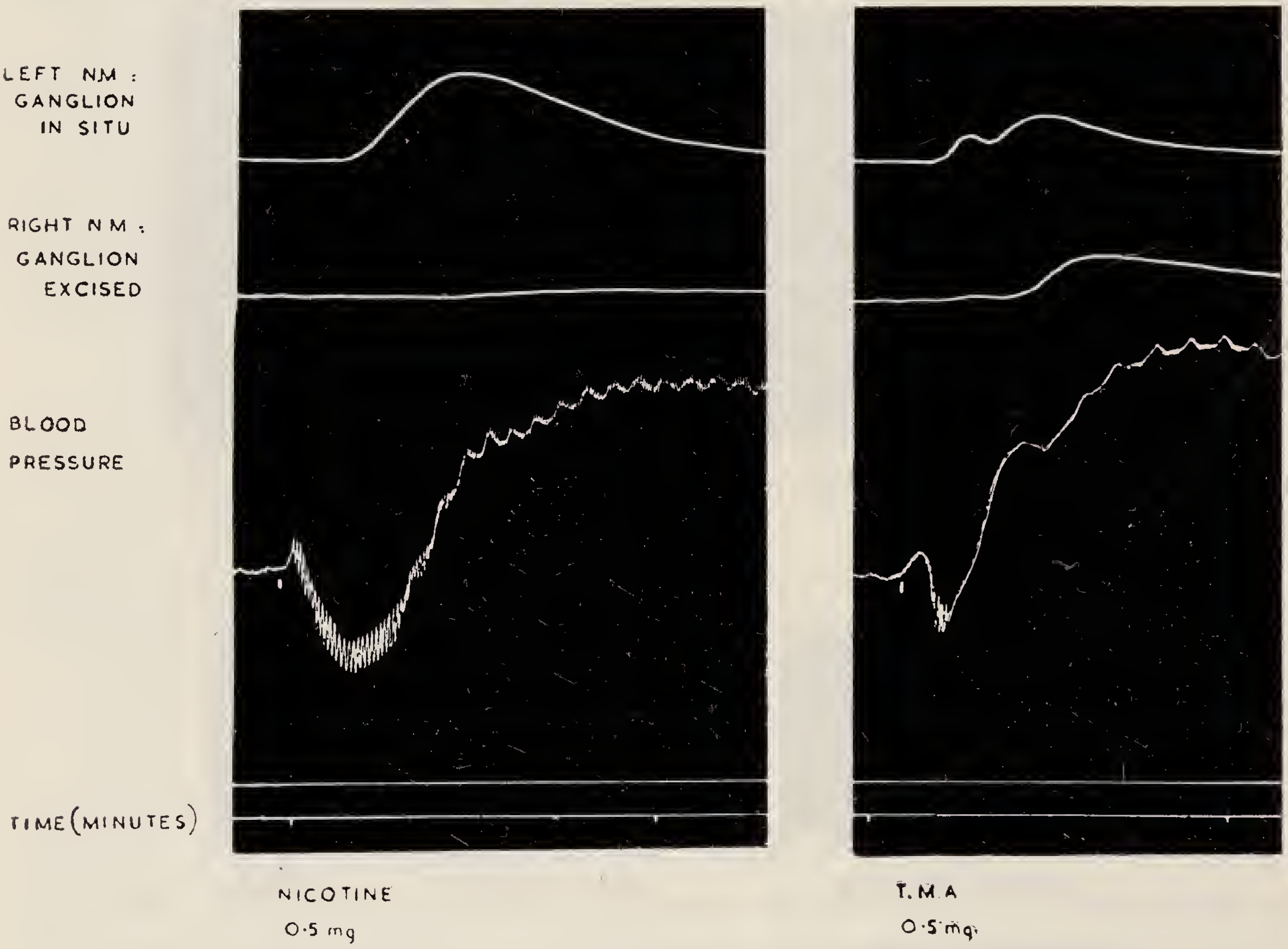


FIG. 2

A method of distinguishing ganglionic and extra-ganglionic actions of a drug.

In the cat anaesthetised with chloralose, the superior cervical ganglion is excised on one side. Records are taken with equally balanced and similar levers from the nictitating membranes on both sides.

On the left is the response of the nictitating membrane to nicotine, which is almost entirely ganglionic. On the right is the response to tetramethylammonium, which has an initial ganglionic component, followed by an extraganglionic action (found later to be greatly reduced by adrenalectomy).

These are only a few of the difficulties one has to face in passing from the easily attained position of suspecting a ganglionic action to characterizing it accurately. It is small wonder that proper pedigrees, so to say, have been established for only a few of the most important substances.

Drugs related chemically to acetylcholine

1. *Depolarization.* First come drugs which resemble acetylcholine so closely at the ganglion as to imitate its action, causing depolarization of the cell-body. If this progresses far enough, the action potential is abolished, and transmission of excitation across the synapse no longer occurs. Perhaps the clearest example of this is provided by tetramethylammonium, whose ability to depress the ganglion action potential runs closely parallel to the ganglion depolarization (PATON and PERRY, 1952).

But a distinction must be made here. With sustained vigorous depolarization the ganglion action potential in response to preganglionic nerve stimulation may be indeed abolished, so that transmission block is complete; but the ganglion is not *inactive*, for it is giving rise to a more or less violent postganglionic discharge. At the endplate, transmission block by depolarization can arise equally readily; but it is accompanied only by a brief period of muscle fibre activation, after which the endplate region becomes inexcitable and prevents the initiation of a propagated response. At the endplate, all types of transmission block lead to quiescence. But at the ganglion it is only competitive block, and not depolarization block, that allows the postganglionic discharge to cease. It is, in fact, hard to recognise how far *transmission* of preganglionic excitation fails at the ganglionic synapse after depolarizing drugs, unless one uses electrical recording, since the stimulant effects of the drug come to take over the tasks of the paralysed transmission process.

2. *Competition.* Second are the drugs which act simply by competing with acetylcholine at the ganglionic synapse. Such a definition immediately raises the question of what is meant, in practical terms, by competitive antagonism. Obviously it is only strictly applicable if one can establish such quantitative relationships between doses of stimulant and antagonistic drugs, as would satisfy the kinetic equations of a competitive process. But this is virtually impossible in practice, so long as biological variation is so much greater than that of physical and chemical systems. One can, however, make a working definition by requiring 1) that the antagonism should be reversible; and 2) that

it may be relieved by increasing the concentration of stimulant drug, and re-established by increasing in turn the dose of antagonist, so that one can proceed as though lacing a shoe with first one lace on top and then the other. There is always an upper limit to the process, when the stimulant drug seems to become relatively ineffective and even sometimes (in the presence of very large amounts of an antagonist) itself depressant, but usually several cycles can be demonstrated. This is still, however, only circumstantial evidence. Suppose one takes a model experiment in which one studies, for instance, the antagonism by a sympatholytic drug to the response of the nictitating membrane to an injection of nicotine; one could quite readily show that the drug would depress the effect of a small dose of nicotine as revealed by the contraction of the nictitating membrane. Then one could show that increasing the dose of nicotine would overcome the antagonism, and so on. To take another example, one might excite a nerve trunk electrically and show that a certain concentration of local anaesthetic applied further down the trunk reduced the effect of a certain sub-maximal stimulation, that by increasing the stimulus strength this antagonism could be overcome, and that by further increasing the concentration of the anaesthetic the antagonism could be re-established. In both these examples, the conditions of our working definition of competitive inhibition are met. But nobody would suggest that a specific sympatholytic competes with acetylcholine or that volts compete with local anaesthetics.

Consideration of these rather elementary examples suggests that one has to be rather cautious in identifying an action as competitive. One's confidence in such an identification can be increased in three further ways. First, by verifying so far as is feasible that agonist and antagonist are acting at the same site; second by requiring some chemical relationship between the two (and for this reason I have segregated drugs chemically resembling acetylcholine in this section); and third by showing that the antagonist in question has a relationship to the agonist in some other way. Thus nicotine in its second phase can be regarded as competing with acetylcholine (although one would hesitate to stress their chemical resemblance) because nicotine displays so many other actions also displayed by acetylcholine.

Any discussion of a possible competitive action requires the mention of one further point. There are a number of observations where a drug is a more effective antagonist against some acetylcholine-like substance than against acetylcholine itself; as for instance the thiazole compounds against nicotine studied by Pick & Unna (1946), or atropine against Compound 2268 F (AMBACHE 1949). It would be convenient if antagonists were uniformly active against a transmitter and its homologues alike. But it is, on reflection, unreasonable to expect it; for if the stimulant drugs differ somewhat in their potency and behaviour, then surely must also their attachments to receptor groups; and it is improbable that such varying attachments would be blocked in identical ways by particular antagonists, even though the main character of the receptor attachment remains the same.

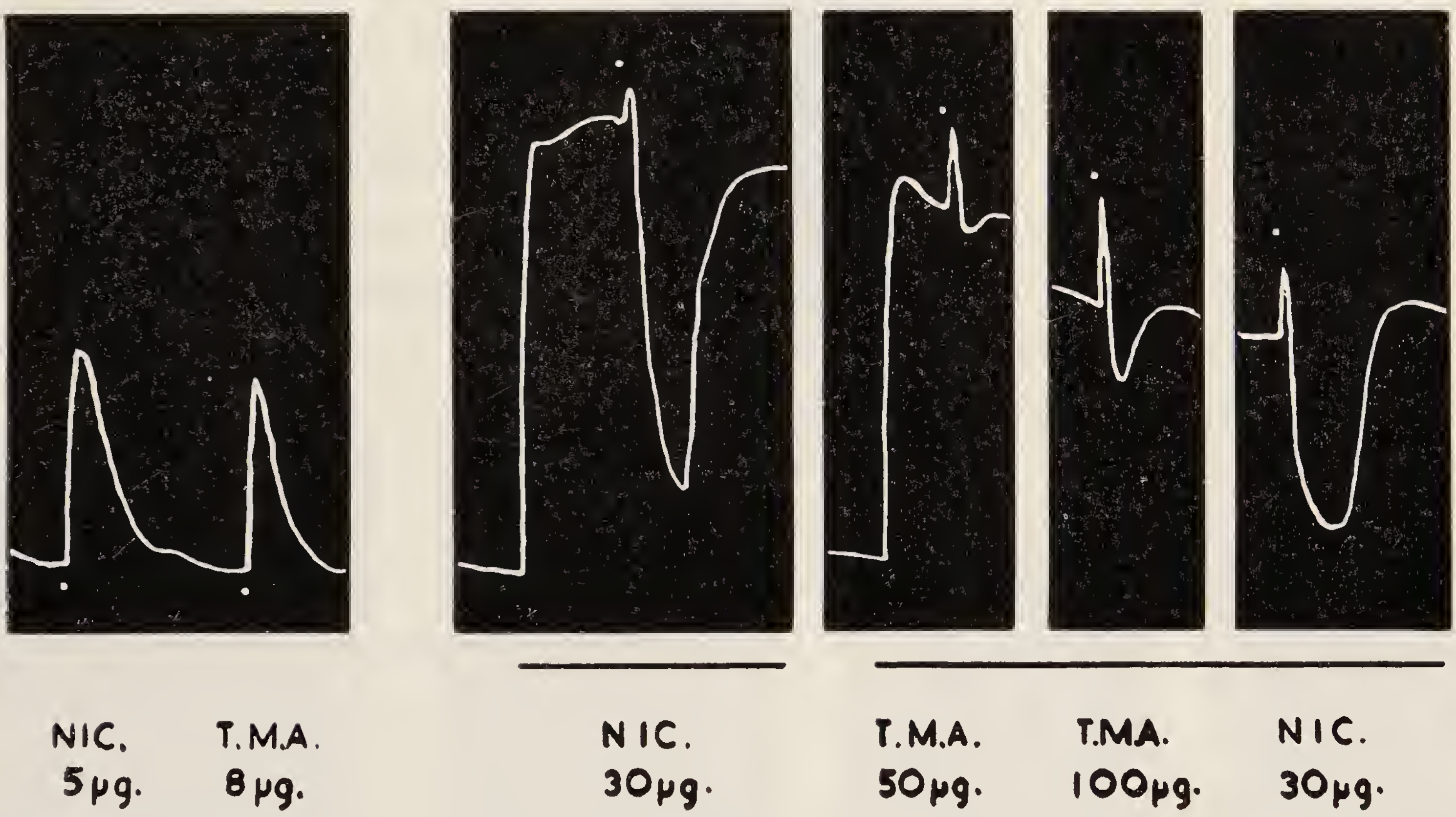


FIG. 3

Effect of ganglion-stimulants on nictitating membrane response to preganglionic stimulation.

A comparison of nicotine and tetramethylammonium tested on the superior cervical ganglion of the cat under chloralose; injections arterially, retrograde into the tied external carotid. Suprarenals removed to eliminate extraganglionic actions.

On the left, contractions of the nictitating membrane due to ganglionic stimulation by roughly equiactive doses of nicotine and tetramethylammonium.

Thereafter stimulation of the cervical sympathetic (maximal shocks at 10 c/s) was applied during the black line, and injections of equivalent stimulant doses of nicotine and T.M.A. again given.

The action of nicotine is accompanied by a transient excitation and a considerable relaxation of the membrane; that of T.M.A. shows chiefly excitation, even with a larger dose.

An interesting group are those drugs which pass from a stimulant to a competitive action, of which nicotine represents the best example. It must be said at once that the only certain identification of an action of this sort at present is by electropharmacological methods, by which it can be shown that the initial stimulation (measured by the ganglion depolarization) has passed off, although the block persists. It may be that other methods of distinguishing this type of drug could be developed, using the evidence that with a more purely depolarizing drug (such as tetramethylammonium) it is difficult to achieve a block of transmission associated with ganglionic inactivity. One could indeed get a shrewd idea of the type of action of a drug by comparing it with tetramethylammonium on the one hand and with nicotine on the other in the cat anaesthetised with chloralose (Fig. 3).

A transitional action of this sort is puzzling to understand in detail. It is rather common in pharmacology, although familiarity has bred the unhelpful term " tachyphylaxis " for some of its manifestations. It is hardly reasonable to hope to understand it properly, however, until we know how any one of the common stimulant drugs work.

3. *Anticholinesterases.* Third, are drugs which owe their effect to an ability to inhibit the cholinesterase in the ganglion. Anticholinesterases are of course very easily identified as such biochemically, but it is not always so easy to demonstrate their action at the ganglion. Sometimes an antagonism to a ganglion-blocking drug can be shown, such as by eserine to *d*-tubocurarine (Chou & Elio 1948) or by DFP or prostigmine to T.E.A. (Kamijo & Koelle, 1952; Reardon et al., 1947) or a potentiation of the effects of preganglionic excitation (Feldberg & Vartiainen, 1934). Electrical recording may be one of the more sensitive methods of demonstrating it; thus eserine has no depolarizing action provided that the rate of stimulation is kept low, but as soon as excitation is increased and acetylcholine can accumulate, then the ganglion depolarization and characteristic change in action potential shape become obvious (Paton & Perry, 1952).

4. *Sensitization.* A particularly interesting compound is m-OH-dimethylethylphenyl ammonium (Tensilon) which drew attention from its high anti-curare action at the motor endplate, combined with a fairly low anticholinesterase activity. Among its actions (it is not a highly specific compound) is that of sensitizing both endplate and ganglion to depolarizing drugs. Figure 4 shows this sensitization for a cat's perfused superior cervical ganglion responding to intra-arterial injections of nicotine.

Bases not closely related to acetylcholine

A good deal of work has focussed on the ganglionic actions of some non-quaternary bases, and it raises certain important problems. A convenient starting-point is the local anaesthetic procaine studied particularly by Harvey (1940) and its more stable analogue procaine amide (Reuse and Bergmann, 1952; Paton & Thompson, 1953), for which—among amines—we have the most complete understanding. Their actions are superficially straightforward : they produce failure of transmission without depolarization or hyperpolarization of the ganglion; and they depress acetylcholine output from the preganglionic endings. But they also antagonise the effects of acetylcholine applied to the ganglion. The first action, preventing transmitter release, is obviously attributable to their anaesthetic potency. But the second action presents much more of a problem. One can take two views about it : the first is that the action is a competitive one, like (for instance) that of hexamethonium or T.E.A. But there are reasons for hesitating over this. The main one is the chemical dissimilarity of the molecules of procaine and acetylcholine. The concept of

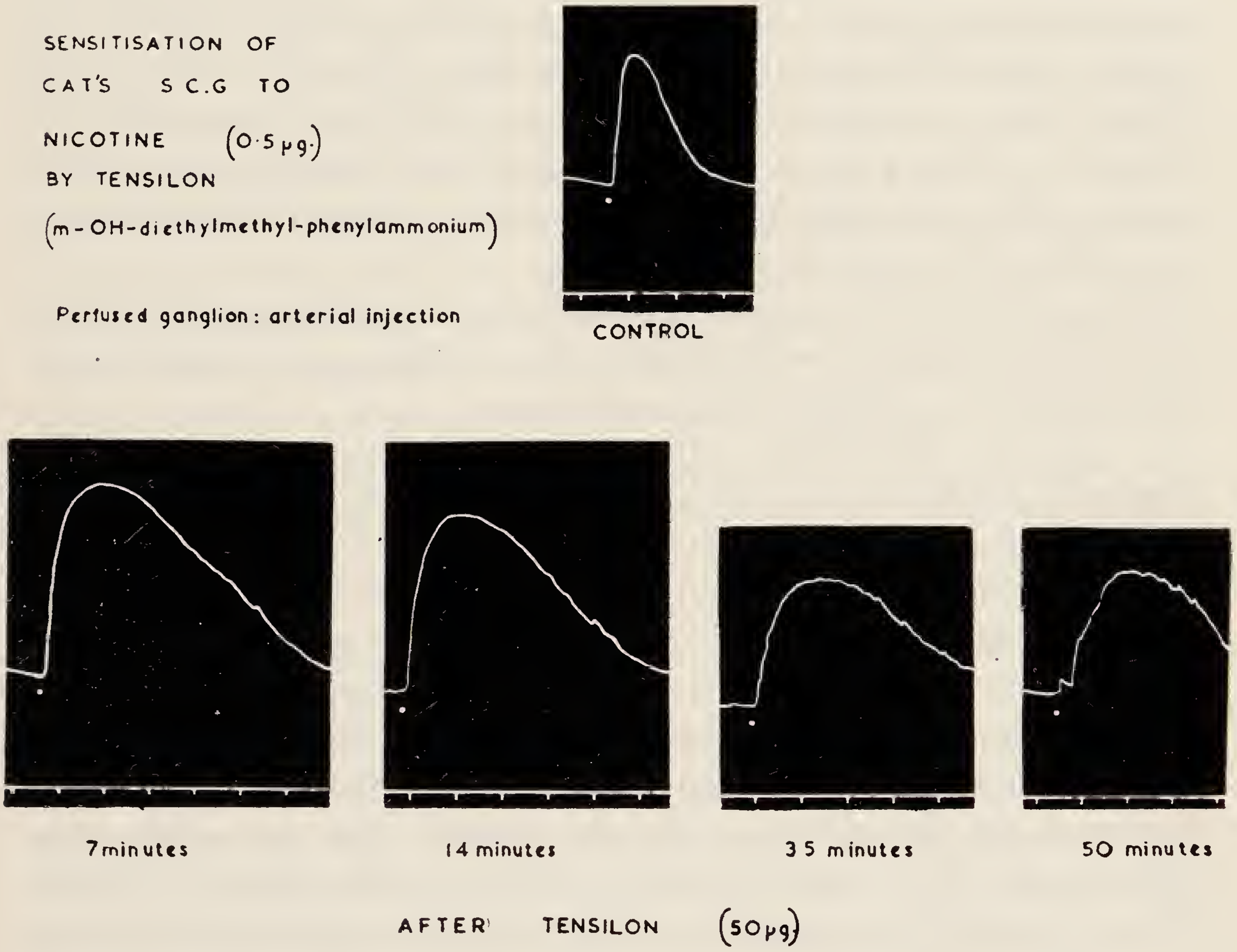


Fig. 4

Sensitization of cat's perfused superior cervical ganglion to nicotine (0.5 μg injected close arterially) by „ Tensilon " (50 μg intra-arterially). Control injection of nicotine above; thereafter the injection was repeated 7, 14, 35 and 50 minutes after the Tensilon. Since nicotine is not attacked by cholinesterase, this augmentation of its effects cannot be due to the anticholinesterase action of Tensilon.

competition is based on such things as the interaction of quaternary salts and acetylcholine at the endplate, of P.A.B.A. and sulphonamides, of histamine and antihistamines, of acetate and fluoracetate—for all of which close structural relationships exist. But if one accepts procaine as a competitor with acetylcholine at the ganglionic synapse, then specific structural relationships are at once sacrificed, and most of those few and slender clues which we possess to the nature of receptor groups—(such as that they are fairly specific reagents for onium salts, and particularly for quaternary nitrogen)—have to be thrown away. One can say, no doubt, that both compounds are " bases ", but one must remember that each belongs to a group already profoundly different from the other in respect of distribution and penetration into the cell.

Further it is worth noting that a comparison of procaine or its amide and hexamethonium, reveals some minor differences in their action, for instance on ganglion action potentials.

2. The second possibility is that these drugs, being local anaesthetics, display this action in two ways at the ganglion, by anaesthetising the preganglionic endings so that they no longer *release* acetylcholine properly (whether by failure of conduction or by interruption of the release process itself), and by anaesthetizing the ganglionic neuronal membrane, so that it does not *respond* to acetylcholine fully; and further, that procaine is perhaps unexpectedly active in this way (when one considers its not very high local anaesthetic potency on nerve trunks) because of the fine calibre of the preganglionic endings and because of the necessarily exposed nature of endings and ganglion cell which allows chemical transmission to take place. If one regards this action as possibly a stabilization of the neuronal membrane, then one is suggesting that local anaesthetics may display their action in several ways; on a nerve trunk (to prevent conduction), on terminals (to prevent release of acetylcholine), and on the receptor membrane of a nerve cell (to prevent chemical excitation)—three diverse manifestations of a single action.

If this second view is sound, then one would expect that other amines—equally unrelated to acetylcholine chemically—should, so far as they are local anaesthetics, also block the ganglion, antagonise nicotinic stimulation of it, and prevent acetylcholine release. Now studies on release are regrettably few, but the association of local anaesthesia, antinicotine action and ganglion block is quite common. *Parpanit* and *Diparcol* for instance block transmission and antagonise the effects of nicotine, and they are quite active local anaesthetics (HEYMANS et al., 1949; BOGDANSKI and KARCZMAR, 1953, HUTCHEON, 1953). *Pantocaine* (KRAUSE, 1951) has been shown to lessen the sensitivity of ganglia to acetylcholine. *Pethidine* and *quinidine*, both (amongst other actions) local anaesthetics (DUTTA, 1949), can produce ganglionic block, and pethidine will block the ganglion to injections of acetylcholine (HEBB & KONZETT, 1949).

With this view of the action of these amines in mind, one can turn to consider three other rather special amines, atropine, eserine and adrenaline. The suggestion that atropine could paralyse ganglia originated in experiments such as those by AMBACHE (1949) in which, on the perfused superior cervical ganglion, he showed that atropine could interfere with the stimulant action of synthetic muscarine-like Compound 2268 F and, in larger doses, could abolish the stimulant effect of acetylcholine. More detailed analysis has confirmed that in fact block of the ganglion can be achieved with atropine, with retention of the response to postganglionic excitation (CAHEN and TUEDA, 1952; GYERMEK & SZTANYIK, 1953; DUTTA 1949; FINK and CERVONI, 1953). But it is also known now that atropine is quite an effective local anaesthetic, about half as active as procaine (DE ELIO, 1947). So that despite the relationship of the drug to acetylcholine peripherally, it may well be that its blocking action depends more on its local anaesthetic action than on a strict competition.

With eserine, likewise, it is interesting to note that 1) it can produce an insensitivity of the ganglion to acetylcholine (FELDBERG and VARTIAINEN, 1934; PATON and PERRY, 1952) without depolarization; 2) it can (under special conditions recently described by PERRY, 1953) depress acetylcholine release; 3) it can interfere with transmission in peripheral nerve (BULLOCK, NACHMANSOHN and ROTHENBERG, 1946; PATON and THOMPSON, unpublished). Despite its dominant anticholinesterase effect, the possibility seems a real one that eserine also has another action, unrelated to its main one, which links it to local anaesthetic amines rather than to quaternary competitive drugs.

The blocking action of adrenaline at the ganglion, described by BURN and BULBRING (1942), for relatively large doses of adrenaline, (facilitation of transmission being obtained with small doses; cf. KONZETT, 1950), and by MARRAZZI (1939), provides a third case of a ganglionically active amine that may be of the same kind. PATON and THOMPSON (1953 *b*) have obtained evidence that adrenaline will depress the release of acetylcholine in the perfused ganglion, and further that adrenaline in a concentration of 300-1000 μg/cc can sometimes depress conduction in the frog's sciatic nerve (after removal of its sheath). It is, however, at most only a rather weak local anaesthetic.

The suggestion that compounds with some degree of local anaesthetic potency should also, by virtue of it, produce the characteristic simultaneous anti-stimulant and anti-release action on ganglia, extends the generalization that such compounds also tend to be quinidine-like, to antagonise acetylcholine on the rectus abdominis, intestine and perfused rabbit's ear, to cool adrenalectomised rats, to depress histamine bronchoconstriction, and to antagonize adrenaline on the rabbit's ear. (DAWES, 1946; BURN & DUTTA, 1948; DUTTA, 1949). It recalls FLECKENSTEIN's classification of many drugs into " catelectrotonic " and " anelectrotonic " (FLECKENSTEIN, WAGNER and GÖGGEL, 1950); but, despite some analogies between anelectrotonus and local anaesthesia, procaine amide does not hyperpolarize the ganglion; so that such a classification is certainly premature at the ganglion. We can only observe that a large number of amines are able to interfere simultaneously with nervous transmission, with ganglionic transmission, and with the ganglion response to chemical excitation by nicotinic drugs; that some of them are known to depress acetylcholine release; and to suggest that all these actions may depend on a common membrane stabilisation, to which the fine terminal ramifications of the preganglionic nerves as well as the adjacent neuronal membrane are particularly sensitive.

C. — *Inorganic ions.*

The simplest compounds active on autonomic ganglia are ions such as *potassium*, *barium* and *ammonium*. (BROWN and FELDBERG, 1936; AMBACHE, 1949; BANISTER, HEBB and KONZETT, 1949). These may act in two ways, either by the excitation of pre-ganglionic terminals so as to cause acetylcholine release (demonstrated for potassium) or by excitation of the ganglion directly. These actions may be distinguished by the fact that the former, but not the latter, is abolished by denervation and by the use of ganglion blocking drugs.

Deficiency of *calcium* (HARVEY & MACINTOSH, 1940) will depress the release of acetylcholine and, at the same time, produce a discharge of the ganglion cell; thus a failure of transmission occurs but post-ganglionic activity is still observed. *Phosphate* compounds, including ATP, exert a stimulant action both on the normal and on the denervated ganglion (FELDBERG & HEBB, 1947) and it has been suggested that they work by calcium deprivation.

Magnesium causes block, and depresses ACH release (STANBURY, 1948; HUTTER and KOSTIAL, 1953).

D. — *Non-basic substances.*

This category includes a number of miscellaneous compounds. First may be mentioned the barbiturates (EXLEY, 1952) some of which may be quite active in interfering with ganglionic transmission; it is not quite established how this occurs but it is probably by depression of acetylcholine release. Second are the important group of general anaesthetics (LARRABEE and POSTERNAK, 1952). Although a number of these are known to interfere with ganglionic transmission, too little is known about the mechanism still. Another group consist of the digitalis glycosides, which KONZETT and ROTHLIN (1952), found to potentiate the effect of acetylcholine on the ganglion.

CONCLUSION

We can now recognize four main groups of ganglionically active substances (and hence four main groups of pharmacological actions) : —

a) *Quaternary compounds*, or compounds closely related to acetylcholine, which *imitate*, *compete with*, *preserve*, or *sensitize to* the natural transmitter. The actions of all these drugs are interpretable in terms of the classical experiments on ganglionic transmission, and are tested usually by repeating certain of these classical experiments.

b) *Amines* which depress ganglionic transmission and antagonize the effects of injected ganglion stimulants, but are also able to interfere with acetylcholine release and to depress nervous conduction. These are a variegated group, not yet properly defined.

c) *Inorganic ions* capable of stimulating or depressing nerve endings or ganglion cell.

d) A *miscellaneous* group including substances such as digitalis, barbiturates, or general anaesthetics.

At least eight types of action must thus be disentangled :

1) Specific ganglion depolarization; 2) Specific ganglion block (competitive); 3) Anticholinesterase action; 4) Sensitization to depolarization; 5) Depression of transmitter release; 6) Antagonism to ganglion depolarization (non-specific); 7) Stimulation of transmitter release; 8) Stimulation of ganglion cells (non-specific direct action). It seems clear that although one thinks at first that the actions of most drugs at the ganglionic level are fairly well understood, it is in fact only a handful of them that have been adequately studied. Our main need,

perhaps, especially in the field of ganglion stimulating drugs or tertiary ganglion blocking agents, is not for the discovery of more such agents, but for the full analysis of those we have.

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